

Lactate Level as an Early Prognostic Marker of Major Adverse Events in Pediatric Open Heart Surgery

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Background --- Elevated lactate levels are commonly encountered in patients after heart surgery secondary to lactic acid production or lactic acidosis due to tissue hypoperfusion and hypoxia during the operation. It provides an important prognostic marker in critically ill patients. This study aims to utilize serial lactate level determinations in predicting major adverse events in children post open heart surgery.

Methods --- Sixty-one (61) pediatric patients who underwent open heart surgery from May to October 2009 were recruited to participate in this prospective cohort study. Blood lactate levels were determined at 4 observational periods: immediately post bypass, 6th, 12th, and 24th hours after surgery. These levels were correlated with outcome (mortality, inotropic score, duration of intubation and ICU stay) and risk factors (bypass and cross clamp time, lowest temperature on bypass). Cut-off level at each observation period was determined using ROC curve, kappa coefficient, sensitivity, specificity and predictive values.

Results --- In this cohort study, mean age of the participants was 7.02 years old, 54% were males and 25 underwent VSD closure. Average bypass and cross clamp time was 120.88 and 81.24 minutes respectively. Post-operative lactate levels correlated significantly with the different outcome measures. The immediate post operative lactate level had correlation with duration of cardiopulmonary bypass; whereas, the 6th hour determination of lactate level was correlated with the lowest temperature on bypass. Analysis of co-variance reported that the lactate levels immediately and 6th hour postoperatively is associated with mortality ($p < 0.001$ and $p < 0.001$ respectively). Trends toward association between 24th hour lactate level and prolonged intubation as well as composite outcome and immediate post operative lactate levels were also established. The following cut-off lactate levels were as follows: ≥ 6 immediate post operatively, ≥ 4 at 6th hour, ≥ 2.5 at 12th hour, and $\geq 24^{\text{th}}$ hours post operatively.

Conclusion --- Numerous studies have documented the significance of lactate level in predicting mortality and morbidity in pediatric heart surgery. With the initial cut off lactate levels determined by this study at four different observation periods and with just a few cardiac centers capable of doing heart surgery, a large, prospective, preferentially multiple institutional trial be conducted in order to clearly established levels predictive of outcome in congenital cardiac surgery in the country.

Phil Heart Center J 2012; 16(2):27-34

Key Words: Lactate levels ■ Pediatric heart surgery ■ Mortality

The term lactic acidosis was coined by Clausen in 1925 but Huckabee was the one who classified it biochemically.¹ "Lactic acidosis is a broad anion gap metabolic acidosis caused by either overproduction or underutilization of lactate."² If the body produces Adenosine Triphosphate (ATP) without the use of oxygen, increase production of lactate ensues. On the other

hand, inadequate removal of lactic acid by oxidation or gluconeogenesis allows underutilization of lactate. Thus, lactate level increases in both surgical and non-surgical instances and has become an important marker in management of critical care cases.

Many researches were done on lactate measurements and their correlation with prognosis

in pediatric cardiac surgery.¹ Blood lactate level has been proven as one of several reliable parameters for hemodynamic evaluation following cardiac surgery. Elevated blood lactate concentration was associated with high morbidity and mortality.³

Utilizing serial lactate level determination as a prognostic marker in pediatric patients who underwent cardiac surgery, clinicians may be able to monitor and predict hemodynamic instability and enable to provide definite intervention long before irreversible shock ensues. With the establishment of several cut-off lactate levels, it may serve as a guide to cardiologists/ pediatric intensivists in the management at different time periods depending on the timing of need for reevaluation of patient's condition within 24 hours after cardiac surgery.

Identification of predictors of outcome is an essential issue for the optimal care of cardiac surgical patients.

Several studies were conducted identifying increased lactate levels as an important prognostic marker of major adverse events in children in the intensive care unit after cardiac operations.

A post operative serum lactate level of greater than 4.2 mmol/L had a positive predictive value of 100% and a negative predictive value of 97% for post operative death in the study done by Siegel et al¹² in 1997. In the same study, lactate levels were also higher in patients who developed multiple organ failure. Elevations in post operative lactate levels reflect intraoperative tissue hypoperfusion. Interventions aimed at improving oxygen delivery with normalization of lactate improve patients' outcome.

Duke et al⁴ in 1997 conducted a cohort observational study determining the physiologic variables that predict major adverse events in children post cardiac surgery. Serial lactate determination on the 4th, 8th, 12th and 24th hour observational periods were conducted and have concluded that blood lactate level of greater than 4.5 mmol/L, decreased mean arterial pressure and duration of cardiopulmonary bypass of

greater than 150 minutes were the significant predictors of adverse outcome following cardiac operation.

Lactate levels of 4 mmol/L during post cardiopulmonary bypass has predicted the severity of outcome in children after cardiac surgery as reported by Shime and associates in 2001.¹¹ Furthermore, significant and sustained elevation of lactate levels were noted on patients who are neonates, with prolonged ICU stay and those who died later in the study. A lactate level of greater than 2.2mmol/L 24 hours after surgery predicted death with a sensitivity of 82% and a specificity of 72%.

A study by Munoz et al⁹ done in 2001 determined lactate levels pre- and post-bypass, as well as upon ICU admission. They have reported the largest increment in lactate level was during cardiopulmonary bypass and a change in lactate level of more than 3 mmol/L had the optimal sensitivity (82%) and specificity (80%) for mortality.

The following variables influenced the post-operative serum mean lactate: age, aortic cross-clamping time, cardiopulmonary bypass time, and the lowest hematocrit during cardiopulmonary bypass.⁸ Lactate levels were extracted during 3rd, 6th and 12th hour after operation and had set 4.8mmol/L as threshold lactate level. The serum lactate levels correlated significantly with inotrope score, intubation time, and ICU stay when multivariate analysis was done.

Cheung PY et al² in 2005 reported that blood lactate levels greater than 4.0 mmol/L during cardiopulmonary bypass was associated with post operative mortality in infants aged 6 weeks or less who underwent cardiac surgery. Postoperative hemodynamic instability occurred in 30% of patients with elevated levels of lactate compared with 10.9% of patients with lower lactate levels.

A study done by Hatherill et al⁷ in 2000 reported that neither admission lactate nor peak lactate levels had association with increasing multi-organ system failure score; although the median peak lactate level

was 5 mmol/L in survivors compared to 6.8 mmol/L in non-survivors, in contrast with other studies reviewed. However, the same study reported that persistent hyperlactatemia 24 hours after admission identified mortality with likelihood ratio of 7.

In one local study done by Gamiao et al⁶ in this institution, serial lactate level determinations were done at 30 minutes post cardiopulmonary bypass, and at 24th and 48th hour upon ICU admission. They reported that serum lactate level of more than 9 post bypass; lactate level more than 7 after 24th hour post-operatively; or a trend toward elevation after the operation is an important indicator of potential mortality and justifies aggressive diagnostic and therapeutic intervention.⁶

This study was conducted to determine the lactate level significant in predicting post-operative morbidity and mortality in pediatric patients with congenital heart disease after surgery.

Methodology

This is a prospective cohort study involving consecutive pediatric patients who underwent open cardiac surgery at the Philippine Heart Center from May 1, 2009 to October 20, 2009. All pediatric patients who underwent closed heart surgery, those without cardiopulmonary bypass and those with inotropic score of more than 15 preoperatively were excluded. An informed consent was given to the parents or guardian prior to inclusion to the study. This study was approved by the Institutional Review Board (IRB).

Lactate levels were determined after bypass, at 6th, 12th and 24th hour after surgery. Blood samples were collected from the patient's indwelling arterial line placed during surgery and a 0.3-0.5ml of blood was drawn into a heparinized tuberculin syringe. Specimen was then brought to pulmonary laboratory and analyzed using Rapidlab 1265 Arterial Blood Gas machine analyzer.

The parameters of clinical outcome

Table 1. Baseline characteristics of pediatric patients who underwent cardiac surgery included in the study (PHC, 2010)

Variables	Frequency or Mean n=61
Mean age (years)	7.02
Gender, Male	33
Type of surgery	
VSD Patch Closure	25
TOF Correction	9
ASD Closure	6
Arterial Switch Operation	5
VSD Closure with infundibulectomy	3
Open Pulmonic Valvotomy	3
VSD Closure with SAM resection	2
Norwood Procedure	2
Mitral Valve Replacement	2
SAM Resection with PDA Ligation	1
Indfundibulectomy	1
LA and LV Mass Excision	1
TAPVR correction	1
Risk Factors	
Mean bypass time (minutes)	120.88
Mean cross clamp time (minutes)	81.24
Mean hypothermic level (°C)	30.3°C

VSD Ventricular septal defect TOF Tetralogy of Fallot ASD Atrial Septal Defect PDA Persistent Ductus Arteriosus, TAPVR Total Anomalous Pulmonary Venous Return

include mortality, inotropic score, duration of intubation and length of ICU stay. *Hospital mortality* is defined as all deaths within 30 days of surgery, irrespective of where the death occurred, and all deaths in the hospital after 30 days among patients who had not been discharged after undergoing surgery. *Prolonged intubation* is defined when intubation exceeds 24 hours after surgery. *Prolonged ICU stay* is defined when duration of ICU stay exceeds 48 hours. Inotrope use was calculated by the inotrope score as follows: *Inotrope score* = (dopamine dose µg/kg per min x 1) + (dobutamine dose µg/kg per min x 1) + (epinephrine dose µg/kg per min x 100) + (milrinone dose µg/kg per min x 10) + (phenylephrine dose µg/kg per min x 100) + (norepinephrine dose µg/kg per min x 100). This formula was adapted from Wernovsky et al.¹²

Table 2. Correlation of outcome with post-operative serum lactate levels at different observation period among pediatric patients (PHC, 2010)

Lactate level versus outcome	n	R	p-value
Duration of Intubation			
Lactate immediate post op	59	0.319	0.014
Lactate at 6 th hr post op	59	0.128	0.336
Lactate at 12 th hr post op	55	0.187	0.172
Lactate at 24 th hr post op	52	0.273	0.050
Duration of ICU stay			
Lactate immediate post op	59	0.336	0.009
Lactate at 6 th hr post op	59	0.063	0.636
Lactate at 12 th hr post op	55	0.142	0.301
Lactate at 24 th hr post op	52	0.173	0.220
Inotropic Score			
Lactate immediate post op	59	0.619	< 0.001
Lactate at 6th hour post op	59	0.631	< 0.001
Lactate at 12 th post op	55	0.053	0.703
Lactate at 24 th post op	52	0.094	0.513

Sample size: At least 59 patients are needed to correlate lactate levels with major adverse events. Calculation is based on level of confidence of significance of 0.05, $\beta = 0.20$ and an assumed correlation incidence of prolonged intubation of 81.2%.

Statistical Analysis: Relationship between clinical outcome and lactate levels were determined using Pearson correlation. Analysis of Covariance (ANCOVA) was used to compare the lactate levels by outcome to adjust the effects of confounders. Analysis of mortality was limited to 2 determinations (post-op and 6th hr) since 3 of the 4 deaths happened within 6 hours after surgery; thereby, no subsequent lactate levels were collected. Intraoperative clinical parameters were used to determine its effect on lactate levels. These factors include cardiopulmonary bypass duration, cross clamp duration and lowest temperature on bypass were analyzed using Pearson correlation. The best cut-off points of lactate levels were determined using Receiver Operating Characteristic (ROC) curve, kappa coefficient, sensitivity, specificity and predictive values

Table 3. Correlation of risk factors with post-operative serum lactate levels at different observation period among pediatric patients (PHC, 2010)

Lactate level versus risk factors	n	R	p-value
Duration of CP Bypass			
Lactate immediate post op	59	0.319	0.014
Lactate at 6 th hr post op	59	0.128	0.336
Lactate at 12 th hr post op	55	0.187	0.172
Lactate at 24 th hr post op	52	0.273	0.050
Duration of Cross Clamp Time			
Lactate immediate post op	59	0.319	0.014
Lactate at 6 th hr post op	59	0.128	0.336
Lactate at 12 th hr post op	55	0.187	0.172
Lactate at 24 th hr post op	52	0.273	0.050
Lowest temp in CP bypass			
Lactate immediate post op	59	0.061	0.649
Lactate at 6th hour post op	59	0.332	0.010
Lactate at 12 th post op	55	0.127	0.355
Lactate at 24 th post op	52	0.053	0.711

at different observational periods.

Results

There are 61 subjects included in this study. The mean age of the participants was 7.02 years; 54% were males; 25 patients underwent VSD patch closure and average cardiopulmonary bypass and cross-clamp time were 120.88 and 81.24 minutes respectively. The mean temperature on bypass was noted as 30.3°C.

The lactate level immediately post-op is correlated with duration of intubation, ICU stay and inotropic score. Also, the lactate level at 6th hour post-op is correlated with inotropic score. (*Table 2*)

The duration of cardiopulmonary bypass is correlated with serum lactate levels immediately post-op. On the other hand, the lactate level at 6th hour post-operatively is correlated with the lowest temperature on cardiopulmonary bypass. (*Table 3*) Mortality is associated with the serum lactate level post-operative and 6th hour post-operative. (*Table 4*)

Discussion

Increased postoperative lactate levels correlated well with the different outcomes (duration of intubation, duration of ICU stay and Inotropic score) with p-values of 0.014, 0.009 and <0.001 respectively. Similar outcome was reported by Basaran et al in 2005.⁸

Inotropic score also correlated well with the 6th hr lactate level with a p-value of <0.001. The rest of the lactate levels did not show correlation with the different outcomes.

Two lactate levels established correlation with the different risk factors. Postoperative

level correlated well with the duration of cardio-pulmonary bypass with a p-value of 0.014 while 6th hour lactate established correlation with lowest temperature on bypass with a p-value of 0.010. The relationship of bypass time with the lactate level after operation was both established by the 2 researches done in the institution.

In order to adjust the effects of confounders, analysis of co-variance was done. The post-operative lactate level of those who died was significantly higher than those who survived with a p-value of <0.001. The same result was shown at 6th hour lactate level post operatively. Lactate levels between prolonged and not prolonged intubation did not differ significantly from each other in all

Table 4. Analysis of Univariate between post-operative lactate levels taken at different time intervals and outcome of pediatric patients (PHC, 2010)

Outcome	Lactate Level							
	Post op		6th hr		12th hour		24th hour	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Mortality								
Dead	16.88	4.70	16.27	1.87				
Alive	6.46	3.56	4.53	2.74				
p-value	<0.001		<0.001					
Duration of Intubation								
Prolonged	7.79	5.14	5.50	3.84	3.45	2.34	2.19	2.26
Not prolonged	6.77	4.42	5.21	4.16	2.60	1.76	1.40	0.52
p-value	0.863		0.669		0.264		0.056	
Duration of ICU Stay								
Prolonged	7.64	4.84	50.8	4.01	3.09	2.75	2.02	2.18
Not prolonged	6.79	4.63	5.54	4.29	2.88	1.90	1.51	0.68
p-value	0.450				0.831		0.376	
Inotropic score								
≥15	14.04	20.99	11.62	16.69	10.19	16.07	10.00	15.89
<15	8.28	7.66	11.84	20.47	5.00	2.27	5.00	2.27
p-value	0.494		0.662		0.747		0.094	
Composite outcome								
Poor	8.08	5.59	5.83	4.67	3.06	2.57	1.98	2.02
Good	5.84	2.56	4.56	2.56	2.86	2.00	1.45	0.58
p-value	0.073		0.186		0.760		0.253	

ICU - Intensive Care Unit

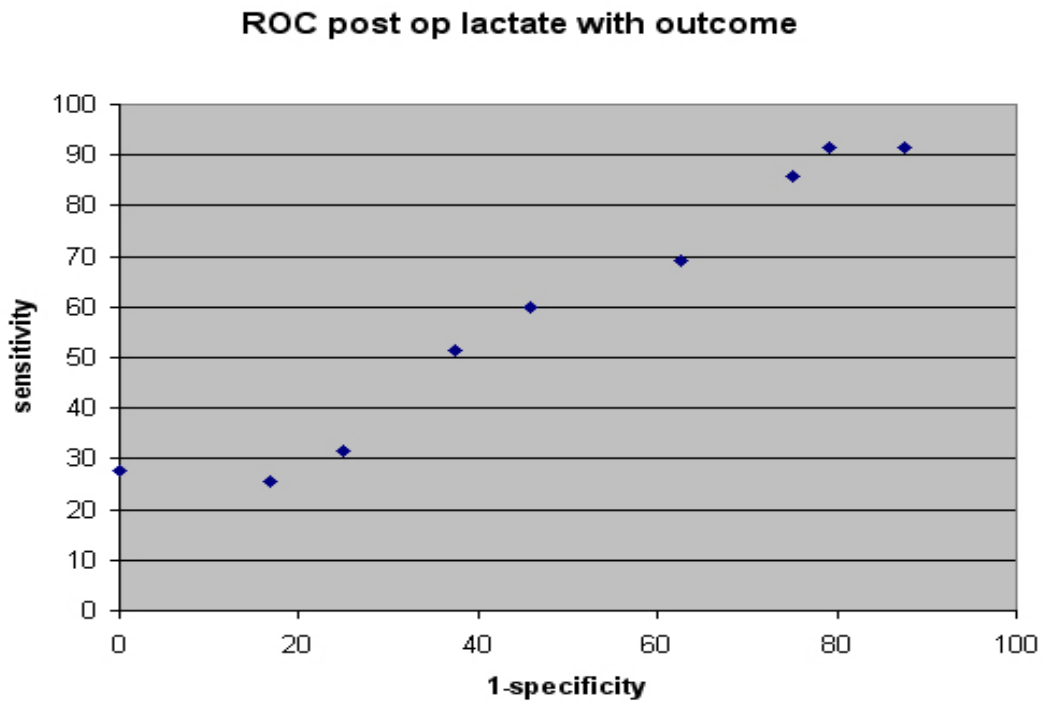


Figure 1. ROC curve of immediate post operative lactate level in relation to outcome of pediatric patients undergoing cardiac surgery (PHC, 2010)

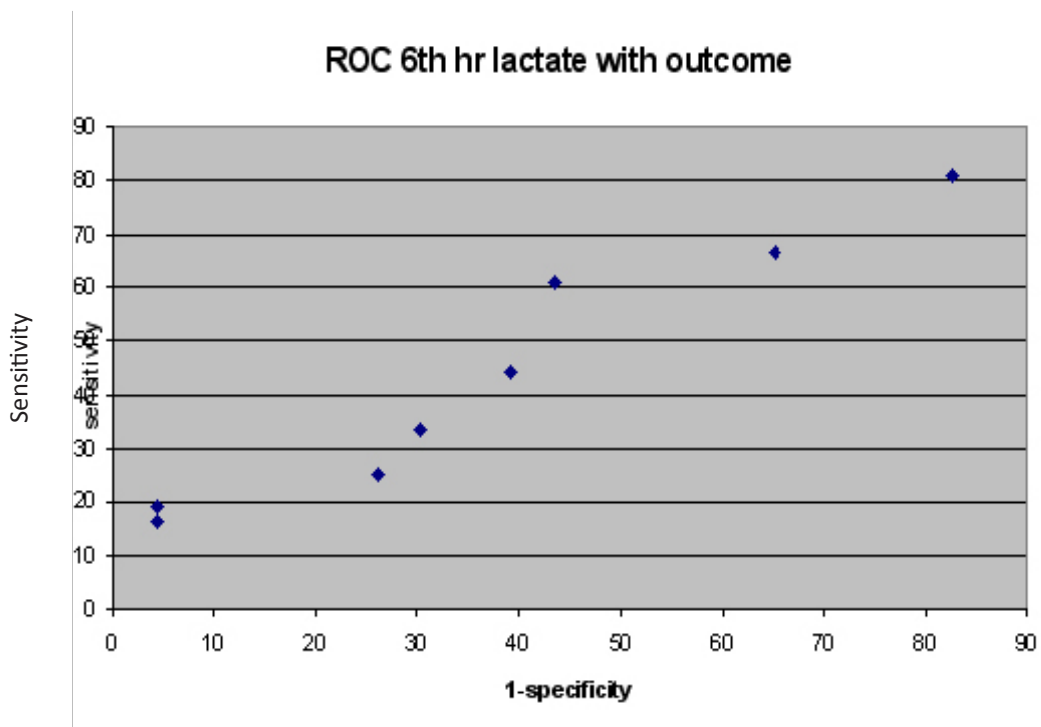


Figure 2. ROC curve of 6th hour postoperative lactate level in relation to outcome of pediatric patients undergoing cardiac surgery (PHC, 2010)

ROC 12th hour lact with outcome

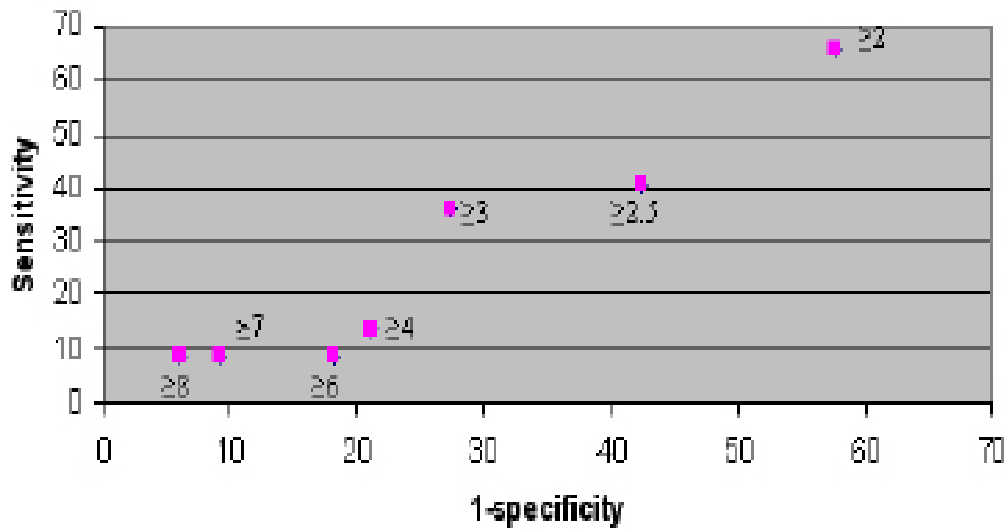


Figure 3. ROC curve of 12th hour post operative lactate level in relation to outcome of pediatric patients undergoing cardiac surgery (PHC, 2010)

ROC 24th hour lactate with outcome

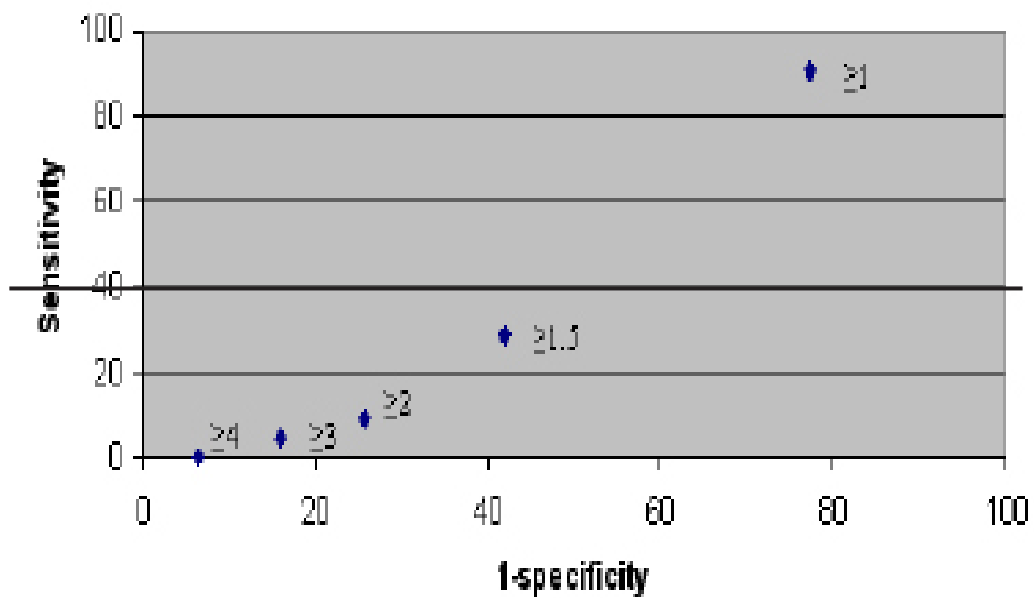


Figure 4. ROC curve of 24th hour post operative lactate level in relation to outcome of pediatric patients undergoing cardiac surgery (PHC, 2010)

observational periods. However, there is a trend of higher lactate among prolonged intubated patients at 24th hour post-operatively with a p-value of 0.056. There were also no significant differences between lactate levels in all 4 time intervals with respect to duration of ICU stay and inotropic scoring. However, during the analysis of composite outcome, lactate level was found to be significantly higher in patients with poor outcome as compared to the other group.

Different cut-off of lactate levels were established in order to predict major adverse events, with highest agreement as determined by the kappa coefficient and the ROC curve, the flex in the following values were computed at different observational periods: ≥ 6 mmol/L post-operatively (Fig. 1); ≥ 4 mmol/L at 6th hour (Fig. 2); ≥ 2.5 mmol/L at 12th hour (Fig. 3); and ≥ 1 mmol/L at 24th hour postoperatively (Fig.4). The post-operative lactate level of ≥ 6 mmol/L was slightly higher than the values reported in other countries, which ranged from 4.2-4.5 mmol/L^{6,10,11} but was significantly lower than the 9 mmol/L cut-off reported by Gamiao et al,¹¹ although the said research focused on mortality as the determinant of outcome. The cut-off 24th hour lactate level of ≥ 1 mmol/L on the other hand, was lower compared to Shime⁶ and Gamiao's¹¹ researches of 2 and 7 mmol/L respectively.

Conclusion

Numerous studies have documented the significance of lactate level in predicting mortality and morbidity in pediatric heart surgery. With the initial cut-off lactate levels determined by this study at four different observation periods and with just a few cardiac centers capable on doing heart surgery, a large, prospective, preferentially multiple institutional trial be conducted in order to clearly establish the lactate levels predictive of outcome in congenital cardiac surgery in the country.

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